Some Topics of Pharmaceutical Research and Development in Japan

journal or publication title	The proceedings of the Hoshi College of Pharmacy
number	18
page range	47-62
year	1976
URL	http://id.nii.ac.jp/1240/00000034/

Some Topics of Pharmaceutical Research and Development in Japan*

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(1) A final filter for reducing particulate matters in parenteral solutions which has been studied by Drs. Horioka and Aoyama.

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A Final Filter for Reducing Particulate Matters in Parenteral Solutions

Particulate matters in intravenous solution have often constituted one of the hazards in using intravenous infusions.

In British Pharmacopoeia and also in the United States Pharmacopoeia, there are descriptions of the limit of number and size of particles in intravenous fluid. A similar standard may be incorporated into the Japanese Pharmacopoeia in the near future.

Dr. Horioka and his group recently have made a detailed study of the particulate contamination regarding the size and the number in infusion fluid[1].

As shown in Table I, five sources can be considered for the contamination of insoluble foreign matters in parenteral solutions. The first one may come from glass containers and rubber stoppers. The second, pottery files as used in Japan in cutting the ampules. The third, contamination in solid parenteral drugs themselves. In these preparations, contaminants enter the product on the process of manufacturing and packaging. The fourth, contami-

TABLE I. Source of Particulate Contamination

1.	Infusion container	:	glass flakes and rubber stopper
2.	Ampule	:	glass fragment, pottery fragment
3.	Solid parenteral	:	contamination in bulk, on dividing process
4.	Infusion set	:	contamination due to insufficient cleaning
5.	Admixture	:	glass and pottery fragment + each particular contamination + contamination of syringe

* Guest lecture at Asian Regional Meeting of the Commonwealth Pharmaceutical Association, Colombo, Sri Lanka, March, 1976.

nation due to the insufficient cleaning in infusion sets. As the fifth, various kinds of contaminants may be introduced in the admixture. We have to pay attention to this problem because the practice of adding several solution into intravenous fluid in the ward is widely available. Here, glass and pottery fragment seem to be the main contaminants. The syringe often performs a carrier of contaminants.

Figure 1 shows the microscopic evidence of contaminants collected by Milipore membrane filters. The photograph "A" shows the contaminants in electrolyte solution, but their origin is not known. "B" shows numerous contaminants in a solid parenteral. Some of them are fibrous substances. Metalic particles are also recognized. Here, the minimum one scale corresponds to 25 microns.

Figure 2 shows scattered glass fragments on the surface of ampules and also the contaminants in infusion sets. Since the pressure inside an ampule is lower than the atmospheric pressure, glass fragments are drawn into the ampule when it is opened. Photograph "B" shows the surface of an ampule scratched with a pottery file and the photograph "C" shows the surface after the fragments were wiped off before opening, as reduced the fragment contamination considerably. The photograph "D" shows some contaminants found in an infusion set. The presence of such large contaminants suggests that infusion sets generally contain various contaminants.

In order to prevent and also to remove these kinds of contaminations, precise handlings should be given on the whole processes of manufacturing and also administration of parenteral solutions. For example, polypropylene or polyethylene bottles, or glass bottles with polyethylene or teflon coated rubber stoppers should be recommended. An improvement in processing of solid parenteral drugs is important, too. This is concerned with an application of freeze-dried process. It should also be considered to use polyethylene ampule and small volume vials.

Hoveve, the most effective method in reducing particulate matters during the administration seems to be the use of final filters. By this device, the contamination after opening the ampule may be kept minimum. The name

A: electlyte solution　　B: antibiotics solid parenteral

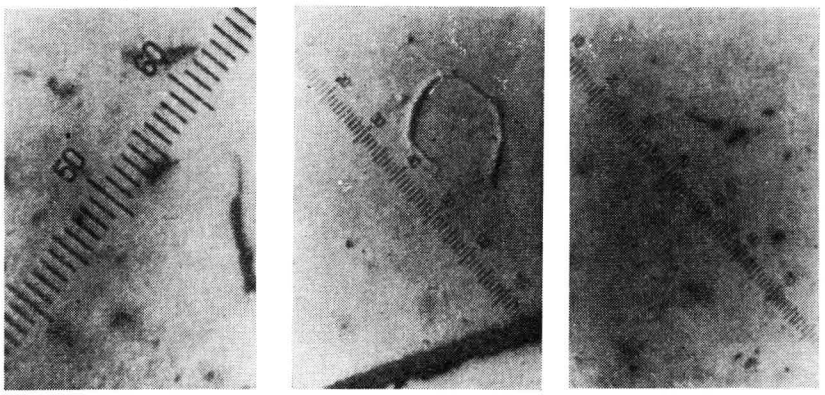


Fig. 1. Particulate Contamination in Infusion and Solid Parenteral.

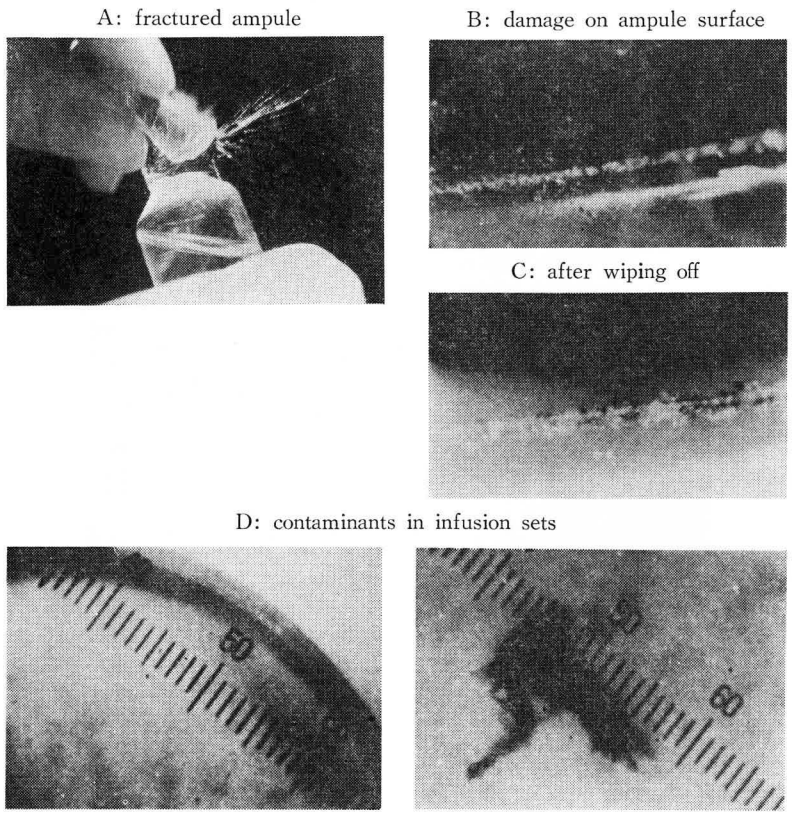


Fig. 2. Glass and Pottery Fragments and Particulate Contamination in Infusion Sets.

"final filter" was given by Dr. Davis several years ago[2], and the merits of this kind of device have been discussed by many workers.

Figure 3 shows the final filter developed by Dr. Horioka and his group[1,3]. It is composed of a polyethylene adaptor of 0.7 by 2.0 centimeters, in which 36 pressed curled pieces of polyester fibers of 3 meters in length are inserted. This filter is set between the syringe and the needle. Any fragment does not come out because each fiber is so long. In order to evaluate the effect of the final filter, they studied the particle size distribution before and after the filtration. As the model experiment, they tried oak charcoal and latex, too. The results shown in Fig. 4 were obtained using a 5 channels HIAC automatic particle counter. The vertical axis here is in logrithmic scale.

The effect of the final filter is shown to be remarkable. In the case of latex particles, the effect was less than the other cases. This may be due to the completely spherical shape of the particles. Actually such spherical particles are not observed in parenteral preparations. Therefore, it can be said that this new final filter has a dramatic effect on reducing particulate matters.

They investigated an optimal length of the fiber, and found the best result was given with the fiber of 3 meters without decreasing the flow rate of fluid, which was shown in Fig. 3. The particles larger than 25 microns are

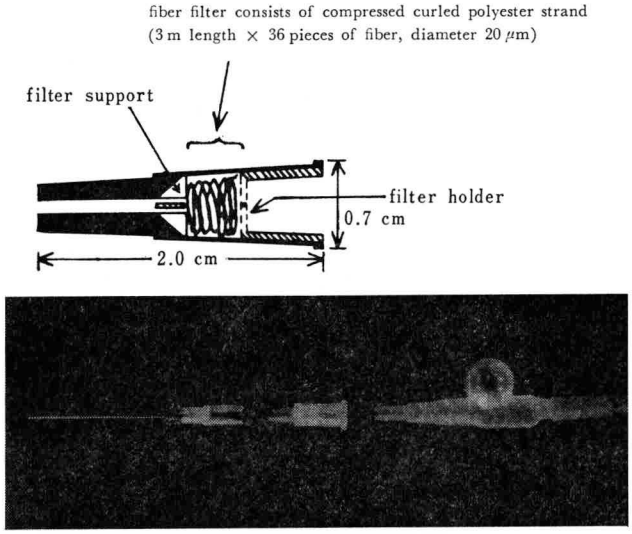
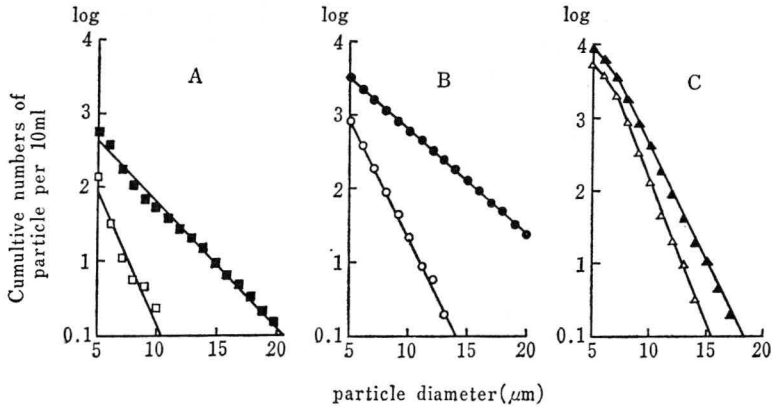


Fig. 3. Constitution of Terminal Ishikawa Fine Filter Unit.



A: Solid parenteral ■●▲ no filter B: Oak charcoal particle (<37 μm) □○△ with filter C: Latex particle (5.7±1.5 μm)

Fig. 4. Particle Size Distribution before and after passing through Filter.

completely removed in infusion solution of commercially available products, as shown in Table II.

Generally, the final filter is designed for the administration of a large volume of intravenous solution. However, it can be used for an injection with syringe, too. If it is desired to remove smaller particles, highly compressed polyester fibers or Milipore filter of glass fiber can be used instead. In Japan, the final filter is getting popular in every class of hospitals.

Polyolefine Bottles for Infusion Solutions. Especially, Polypropylene Bottles

Plastic containers have been widely used in pharmaceutical field, owing to the progress in

TABLE II. Removing Effect in Infusion of Solid Parenteral

Solid parenteral*	Fine filter	HIAC method** (particle in 1 vial) 5−10	10−25	25−50	50−100	>100 μ	Microscopic method*** >100 μ
A 635mg	on filter	21464	2258	95.8	5.6	0	29
	with filter	5628(73.8%)	71(96.8%)	0	0	0	
B 5g	no filter	22184	1551	55.6	5.6	1.4	24
	with filter	1306(94.1%)	87(94.1%)	0	0	0	
C 250mg	no filter	8368	708	37.5	2.8	0	8
	with filter	2472(70.5%)	60(91.5%)	0	0	0	
C 250mg	no filter	5237	644	38.9	1.4	0	2
	with filter	437(91.7%)	28(95.7%)	0	0	0	
Control (0.9% NaCl. in Polypropylene)	no filter	370	60	5.0	0	0	0
	with filter	25	5	0	0	0	

* Solid parenteral dissolved in 500 m*l* isotonic sodium chloride solution in polypropylene made by biaxially streching method.

** Particle number is the mean of three samples, 1 sample was measured 6 times.

*** Particle number is the mean of three samples.

plastic industries.

Among the containers for infusion solutions, there are various styles of plastic bottles.

Plastic bottles have various merits. With the view of manufacturing, they are suitable to the quality control, espicially, to the automatic processing of filling of the solution and of packaging. Also they are convenient in trasportation both at commercial market and in hospital because they are not beakable. In the same meaning, they are convenient in clinical use, too. And they are easy for disposing after use. Moreover, little particulate contamination is expected compared with glass bottles. This is an important point, as mentioned previously.

On the other hand, they have some demerits. If such substance as plasticizer is added, it may come out in solution. Such interaction as adsorption of drug from solution may take place. Vapor or gass may permeate into the bottle. It is difficult to look inside the bottle because of the low transparency compared with glass bottles. Sometimes, a deformation may take place because of low heat-resistance. However, these problems can be almost solved. Especially polyolefine bottles have much merits overcoming the demerits.

According to the experiment of Dr. Horioka[4], the extract of polyvinyl chloride bottle showed a considerable UV absorption, as shown in Fig. 5. Moreover, the absorption curves differed with the variety of polyvinyl chloride. This result may be based on the difference in the kind of additives. Any absorvance is hardly observed in such polyolefine as polypropylene and polyethylene.

Generally, polyolefine has a good plasticity itself. Therefore, it does not need any plasticizer for molding, and thus sometimes it is called "pure plastics". That may be the reason why polyonefine bottles release less amount of substance in solution.

Among polyolefine bottles, here will be explained polypropylene bottles developed by Otsuka Pharmaceutical Company, which is

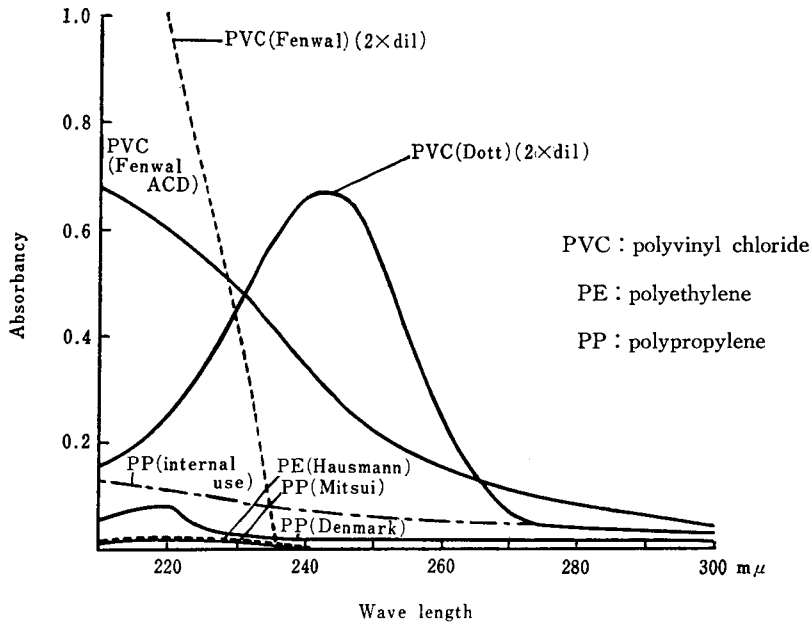


Fig. 5. UV Spectra of Aqueous Extract of Plastic Containers.

named "Plabottle[5]".

Actualy the product is commercially available, but the details of manufacturing process are not disclosed because many of them belong to the company's know-how. Anyway, the product has excellent properties as a container for infusion solutions.

When Plabottle is tested according to the methods for plastic containers described in Japanese Pharmacopoeia, United States Pharmacopoeia and British Pharmacopoeia, it meets all the requirements.

According to the intracutanious reactivity test using albino rabbits, both extracts with normal saline and with alcohol plus normal saline gave no tissue reaction as well as blank solution. The haemolysis test of the extract with normal saline using the fiber-free blood rabit was negative as well as blank. The implantation test using the muscular tissue of the paravertebral site of rabbit was also negative as well as USP Negative Control Plastic Reference Standard.

Plabottle is made of polypropylene by blow molding of biaxial orientation, and thus it is produced as a good transparent container for infusion solution. Compared with glass bottle in transparency at 450 nm, Plabottle was as nearly transparent as glass bottle: glass bottle $93.16 \pm 2.94\%$; Plabottle $88.96 \pm 1.69\%$, in comparative transparency.

When Plabottle was tested according to the method of microbial permeability test described in Swiss Pharmacopoeia, the result proved that Plabottle is resistant to microbial passage. Following Swiss Pharmacopoeia, 5% glucose solution and Ringer's solution were filled in Plabottles, respectively, then sterilized, and incubated in bouillon medium to which *Serratia marcescens* was inoculated. After 8 days, any

bacterial growth was not observed. According to the sterility test described in Japanese Pharmacopoeia also, the result was negative.

According to the stability test, sodium lactate injection, dextrose and sodium chloride injection, normal saline injection and intraperitoneal solution bottled in Plabottles were all kept stable at room temperature for 2 yers, and at 40 or 50° for one year. For example, content, pH, purity, pyrogenicity, sterility, particulate matters and weight change are kept stable and have no problem.

Figure 6 shows the change of pH of physiologic saline solution in comparison with rubber stoppered glass bottle. In Plabottle, pH was kept almost the same for two years, while in the rubber stoppered glass bottle pH rose gradually. In the rubber stoppered glass bottle, some alkaline substances may come out in solution, which probably cause the pH rise.

As shown in Fig. 7, any particulate matter did not appear in physiologic saline solution in Plabottle, while in rubber stoppered glass bottle, particulate matters appear after 6 months and subsequently increased remarkably. The

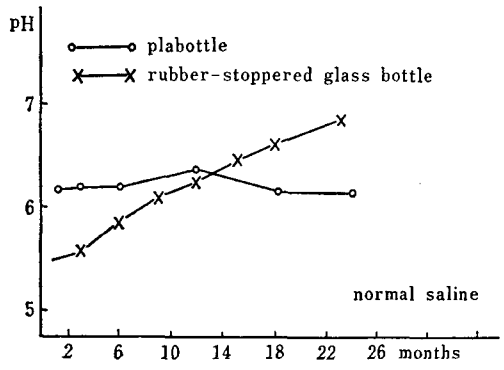


Fig. 6. Change of pH of Physiologic Saline Solution in Plabottle and Rubber Stoppered Glass Bottle.

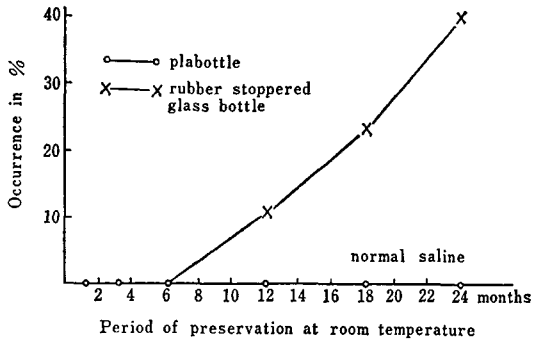


Fig. 7. Occurrence of Particulate Matter.

vertical axis is given in frequence of occurance. So it can be said that in rubber stoppered bottles, particulate matters were observed in nearly half of bottles after 2 years' preservation.

It has been generally accepted that particulate matters appear in the solution in rubber stoppered bottles after a long time. This is substantially due to the nature of rubber stopper of glass bottle. Various additives in the rubber stopper or intrinsic substances in glass can be eluted or deposited into solution, and they may appreciate to form a visible mass of particles with the lapse of time.

From these results, it can be understood that Plabottle afford a very available means as the container for infusion solutions. Now in Japan, Plabottle is recognized to be at the highest level.

Some Dissolution Studies of Solid Pharmaceutical Preparations. Inclusion Compounds of Drugs with Cyclodextrins

When a drug is administered, the drug effect generally depends on the bioavailability. The bioavailability of drug is defined as the amount and the rate of drug taken into the dody.

And this may often differ among the different preparations of the same generic name. The most famous example is the chloramphenicol palmitate preparation.

A problem of the difference in bioavailability of drug generally arises in such solid preparations as powders, capsules, granules and tablets. Usually the drug in solution is absorbed fast because the interfacial area of gastro-intestinal tract which is effective for the absorption of drug in body, is very large. In the case of human, this area is said to be almost as large as a tennis court. Therefore, the dissolution of particles of drug performs a rate determining step in the absorption of drug. In other words, this affects the bioavailability of drug.

Actually there are many reports to show that the bioavailability is related to the dissolution rate of drug. Figure 8 shows the data of various aspirin preparations by Dr. Levy[6]. When the same amount of aspirin is administered orally, the absorption rate increases with the dissolution rate.

A chemical compound often has different crystalline forms, such carbon and diamond. This kind of phenomena is called polymorphism. In the case of drug, there has never been found such a difference as between carbon and diamond. However, chloramphenical palmitate mentioned already has four different crystalline forms, for example.

Figure 9 shows two different crystalline forms of aspirin give different absorption curves. The two polymorphs were obtained by Dr. Tawashi of the University of Montreal[7], Polymorph II has about 70% higher bioavailability.

Examples mentioned already show the importance of dissolution studies of pharmaceutical preparations.

For the studies, the dissolution of intact active ingredient should be considered first. The important factors in this study are: particle size, crystalline form, and solubility of powder, and such testing conditions as temperature, stirring speed, volume of test solution

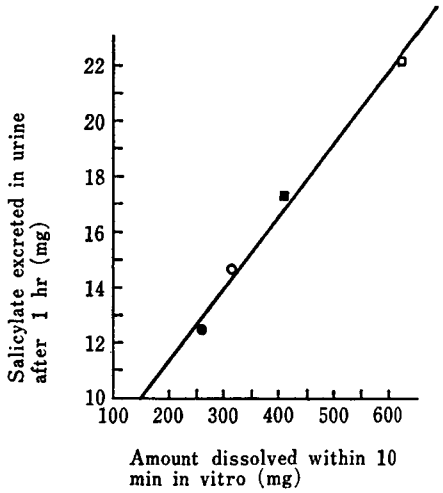


Fig. 8. Various Preparations of Aspirin.

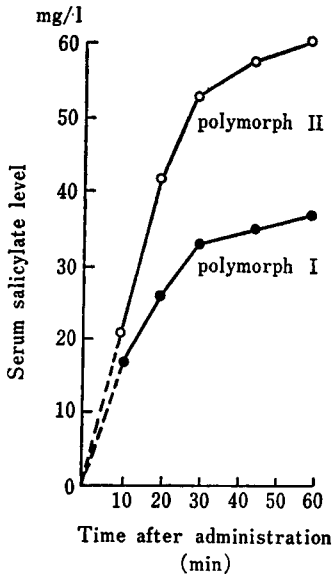


Fig. 9. Absorption of Two Polymorphs of Aspirin.

and so on.

Second, the release of drug from the preparation should be studied. This is especially important from the practical point of view. For this, the stirring apparatus and analytical apparatus should be developed. Of course, automatical ones are preferable. And the appropriate test solution should be investigated, regarding pH and ionic strength of the solution, which give influence on the dissolution rate. Especially for coated preparations, not only pH, but also ionic strength is important.

Third, the correlation between *in vitro* result and clinical effect should be studied. As is well known, this is important in developing an available method of dissolution test.

Various methods for dissolution test have been investigated by many workers.

Figure 10 is the apparatus for the dissolution test described in United States Pharmacopoeia and National Formulary. There is a rotating basket including test sample. The sample solution is taken out from the tube. In Japan, any dissolution test is not described in pharmacopoeia right now. But it will be included in a revised pharmacopoeia before long. Now a research project of Ministry of Welfare is working to investigate the type of apparatus and the testing conditions.

The USP method is suitable to obtaining the rate of release of drug from a preparation. But it is not suitable to obtaining the intrinsic dissolution rate of active gredient of drugs.

In order to obtain the intrinsic dissolution rate very precisely, we devised a method using a rotating disk and have applied to the analysis of dissolution phenomena of drugs[8]. For the rotaing disk method, we should make a disk of a given surface area, using special die and punches. However, it sometimes acompanies a difficulty of making a disk of drug powder. For example, the compressed disk is often broken when it is taken out of the die. Then, we devised another apparatus for dissolution experiment using a stationary disk, following Dr. Millosovich, as shown in Fig. 11[9]. A given amount of drug powder is compressed in a cylindrical die. This die and disk is put in the cavity of the holder. The disk is made face toward the stirrer, and the opposit site of

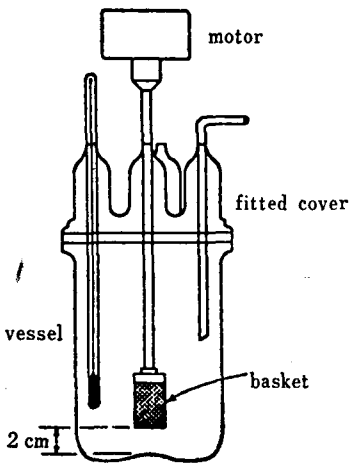


Fig. 10. Apparatus for Dissolution Test of U.S.P. XIX.

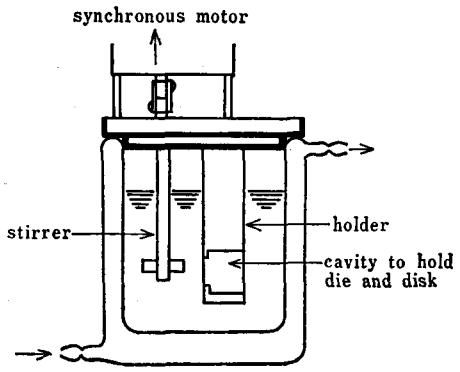


Fig. 11. Dissolution Apparatus by a Stationary Disk Method.

the die is stoppered. The dissolution of drug in the solution is measured under a given stirring condition at a given temperature controlled by circulating constant temperature water.

The method mentioned here is widely applicable to the dissolution studies of active gredients of drugs. For example, the intrinsic dissolution rate of polymorphs can be determined. Generally speaking, polymorphs are called phase I, form I, or phase A or B, like that. Barbital gives three polymorphs which are recognized by IR absorption spectra (Fig. 12) and X-ray diffrection patterns[10]. Phase II easily changes to Phase I by compression. Phase III dissolves fast compared with phases I and II.

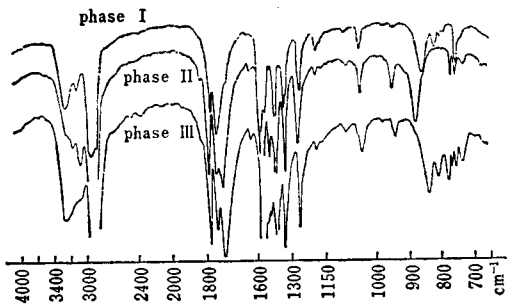


Fig. 12. Infrared Absorption Spectra of Barbital Polymorphs in Nujol.

We got four polymorphs of oxytetracycline[11]. Figure 13 shows their X-ray diffraction patterns. Phase II has a strong tendency to changing to Phase I.

Phase III of oxytetracycline dissolves fast, as shown in Fig. 14. As explained already, these curves were obtained for the powders of the same surface area.

We found that phenylbutazone, an antiinflammatory drug, has three polymorphs, as shown by X-ray diffraction patterns in Fig. 15[12]. Phase II of phenylbutazone dissolved faster than phase I at every different temperature, as shown in Fig. 16.

In that connection we found an interesting phenomenon. Phase III of phenylbutazone is usually changed to phase II or phase I by compression. However, this change was suppressed with the addition of 5% of stearate, and dissolved faster than any of phases I and II, as shown in Fig. 17[13]. Stearate generally has a water repellent property. Therefore,

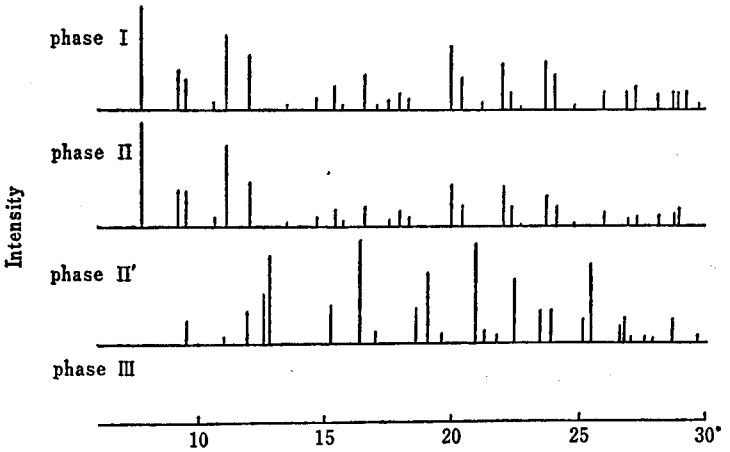


Fig. 13. X-Ray Diffractograms of Polymorphs of Oxytetracycline by Cu-Kα Radiation.

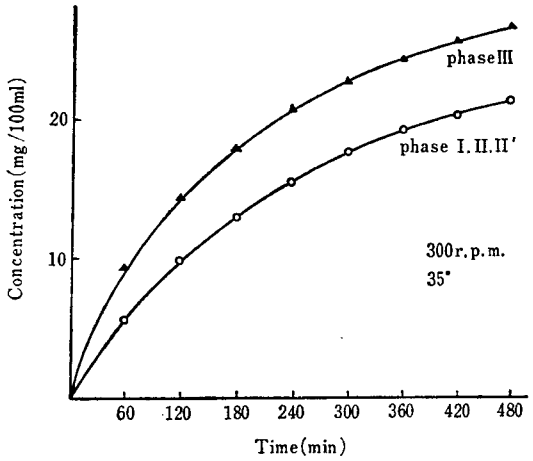


Fig. 14. Dissolution Curves of Oxytetracycline.

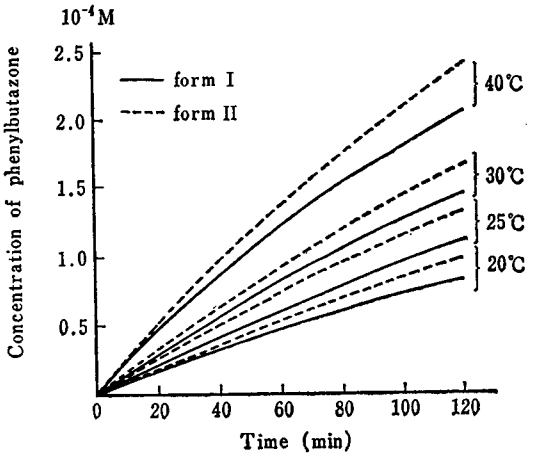


Fig. 16. Initial Dissolution Curves of Phenylbutazone Polymorphs in 1/30 M Phosphate Buffer Solution at pH 7.5 at Various Temperatures by Stationary Disk Method.

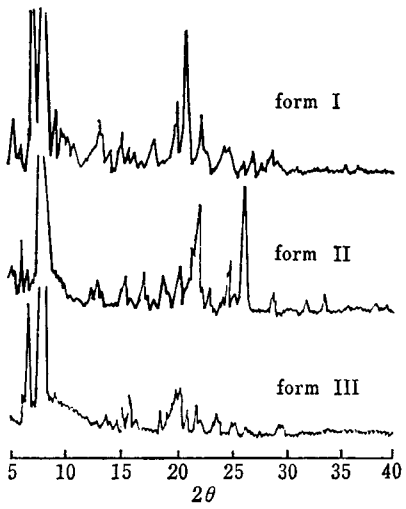


Fig. 15. X-Ray Diffraction Patterns of Phenylbutazone Polymorphs by Cu-Kα Radiation.

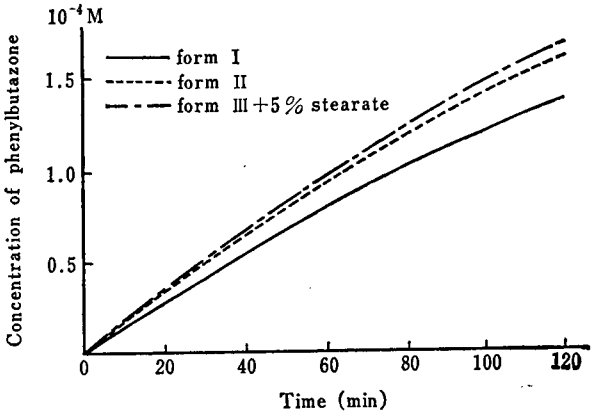


Fig. 17. Initial Dissolution Curves of Phenylbutazone Polymorphs in 1/30 M Phosphate Buffer Solution at pH 7.5 at 30°C by Stationary Disk Method.

the intrinsic dissolution rate of phase III of phenylbutazone may be much larger than that shown in this curve. Anyway, it is suggested that some additive is useful for supressing the phase change of crystal by compression.

P-Hydroxy benzoic acid and phenobarbital have the respective hydrate forms. Usually andydrate dissolves fast and gives such a maximum in the dissolution curve as shown in Fig. 18[14]. This maximum part corresponds to the over-saturation and thus crystals come out.

But when the anhydrate is administered in the body, the absorption is faster than crystallization. Therefore, this type of anhydrate

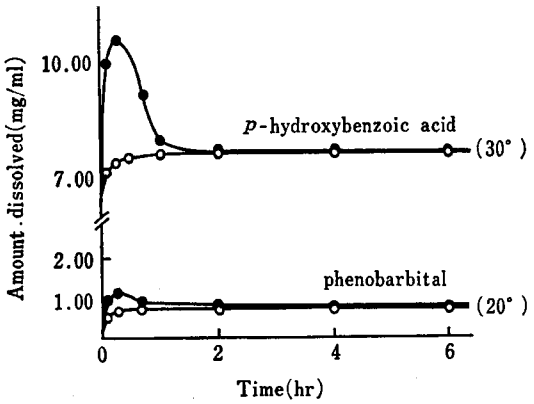


Fig. 18. Dissolution Behaviours of Anhydrate and of Its Hydrate by Dispersed Amount Method.

sample amount: *p*-hydroxybenzoic acid 0.7 g phenobarbital 0.2 g in 50 m*l* water
-●-: anhydrate -○-: hydrate

may give a high bioavailability.

Mathematical analysis of these curves give two rate constants: One for diffusion of molecule in solution; another for crystallization of oversaturated portion when anhydrate dissolves. Moreover, two saturated concentrations or solubilities are obtained: one for hydrate (C_{SA}); another for anhydrate(C_{SH}). The data are shown in Table III and IV. The saturated concentration of solubility for anhydrate is just theoretical one, which is not obtained by usual solubility measurement. This is one of the characteristic points of dissolution rate study.

TABLE III. Saturated Concentrations, C_{SA} and C_{SH}, and Values of $C_{SA}-C_{SH}$ of *p*-Hydroxybenzoic Acid at Various Temperatures

Temperature (°C)	Anhydrate C_{SA}[a)]	Hydrate C_{SH} (mg/m*l*)	$C_{SA}-C_{SH}$
40	16.62	12.90	3.72
35	13.51	10.01	3.50
30	10.76	7.65	3.11
25	8.62	5.97	2.65

a) Values estimated from disoslution curves.

TABLE IV. Saturated Concentrations, C_{SA} and C_{SH} and Values of $C_{SA}-C_{SH}$ of Phenobarbital at Various Temperatures

Temperature (°C)	Anhydrate C_{SA}[a)]	Hydrate C_{SH} (mg/m*l*)	$C_{SA}-C_{SH}$
30	1.51	1.41	0.10
25	1.32	1.16	0.16
20	1.13	0.73	0.21

a) Values estimated from dissolution curves.

Anyway two different saturated concentrations corespond to the respective chemical potentials of different crystalline forms.

Phenobarbital forms a complex with polyethylene glycol (PEG). Figure 19 shows the X-ray diffraction patterns of the respective components and the complex: PEG 4000; phenobarbital; PEG 4000-phenobarbital complex[15)]. The complex is slightly soluble in water.

This kind of complex formation should be considered in pharmaceutical formulations. Such a complex gives sometimes a good effect,

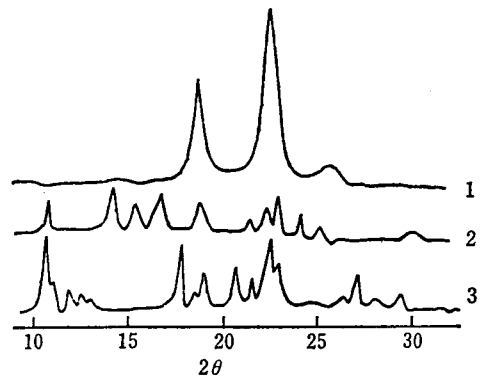


Fig. 19. Powder X-Ray Diffraction Patterns of PEG 4000, Phenobarbital and PEG-Phenobarbital Complex by Cu-Kα Radiation.

1: PEG 4000 2: phenobarbital
3: PEG 4000-phenobarbital complex

sometimes a bad effect. As a good effect, it may afford some means for developing a sustained release preparation.

Before finishing, here will be explained inclusion compounds of slightly water soluble drugs with cyclodextrins as an example of soluble powder preparation[16]. Cyclodextrin (CD) or another name Schardinger dextrin consists of several residues of D-glucose attached by α-1-4 linkage to form a cyclic molecule.

According to the size of molecule, there are three kinds of CD. They are α, β, and γ as shown in Fig. 20. Among them, we can get α and β-CD commercially. β-CD is most available.

CD includes various kinds of molecules in the tunnel. Sometimes the whole molecule and sometimes a part of molecule is included according to the size and functional group of molecule. This kind of inclusion compounds generally gives a good solubility. Drs. Fröming and Weyerman obtained the adducts of β-CD with salycilic acid, benzioc acid, menadion and phenobarbital in solid state by cocrystallization or coprecipitation[17]. These adducts were all highly soluble in aqueous media. From the pharmaceutical point of view, if an inclusion compound of a certain drug with CD is provided in solid state, it may afford a preparation for oral use, which is well soluble in gastrointestinal fluid and also may suppress such an adverse reaction as the irritation of stomach.

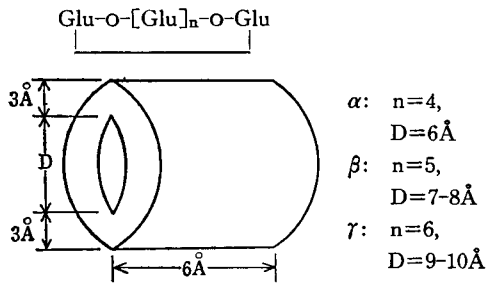


Fig. 20. Cyclodextrins.

We attempted some study to obtain the inclusion compounds of non-steriodal antiinflammatory drugs and additionally other slightly water soluble drugs with α- and β-CD in solid powdered form.

Non-steroidal antiinflammarory drugs are generally very slightly soluble in water and also sometimes cause an adverse reaction due to a stimulant property to stomach upon oral administration. The preparation of inclusion compound was tried also by the coprecipitation method in comparison with the freeze-drying method. According to the coprecipitation method, a drug in ether and CD in water were mixed together with the molecular ratio 1 : 1. This procedure followed the most general coprecipitation method to prepare inclusion compounds. According to the freeze-drying method, a drug and CD with the molecular ratio 1 : 1 were dissolved in aqueous solution containing a small amount of ammonia because the drug are slightly soluble and acidic. Of course, ammonia was not detected in the final product. The products by both methods were washed with ether, and thus if the drug was not included, it was not detected in the aqueous solution of the final product.

The examination was done using thirteen kinds of drugs. The results are shown in Table V.

The freeze-drying method was successful in in obtaining the inclusion compounds of all the thirteen test drugs with β-CD. On the other hand, four drugs among thirteen were included in solid state also by the coprecipitation method. A clear explanation was not given for the reason why the drugs other than

TABLE V. Amounts of Drugs Included by CD (mole/mole of CD)

Drugs	CD	Coprecipitation	Freeze-drying	Drugs	CD	Coprecipitation	Freeze-drying
Indomethacine	β	0	0.92	Ibuprofen	β	0.36	0.82
Azapropazone	α	0	0.97	Ketoprofen	β	0.39	0.72
Azapropazone	β	0	0.90	Anthranic acid	β	0.23	0.95
Phenylbutazone	α	0	0.94	Barbital	β	0	0.61
Phenylbutazone	β	0	0.87	Phenobarbital	β	0	0.83
Flufenamic	β	0	0.83	Sufisoxazole	β	0	0.95
Mefenamic acid	β	0	0.96	Sulfathiazole	β	0	0.98
Ibfenac	β	0.43	0.79	Methylsalicylate	β	0.73	—

the four were not included by β-CD by the coprecipitation method. But when we estimated the molecular sizes by assembled molecular models, those of the four drugs seemed fittable to the cavity of β-CD.

Regarding the amount of drug included, the freeze-drying method gave a very good yield for all the test drugs. Six drugs among them were included almost in 1 : 1 molecular ratio. On the other hand, the four drugs which were included by the coprecipitation method gave a low yield compared with the freeze-dried one. This result suggested that if the drug molecules are partly included in solution, they are easily solidified by the freezing procedure.

In our previous paper, we reported that such drugs as azapropazone and phenylbutazone were included also by α-CD in aqueous solution[9]. When the freeze-drying method was applied to these drugs using α-CD, giving a good yield.

Figure 21 shows the IR spectra of the physical mixture and the freeze-dried one of flufenamic acid with β-CD, for example. A remarkable change was observed in the band at 1650 cm^{-1} which is due to the carbonyl group. This band in the physical mixture hided itself in the freeze-dried one, as shown by the solid

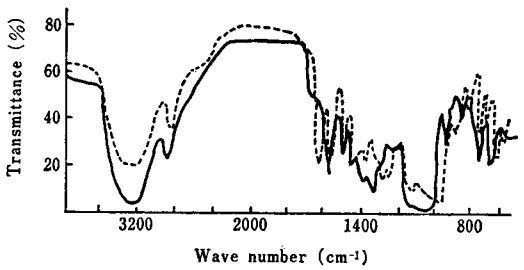


Fig. 21. IR Spectra of Physical Mixture (----) and Freeze-dried Product (——) of Flufenamic Acid with β-CD.

curve. A similar tendency was observed in the coprecipitated inclusion compounds, but it is not so remarkable because the amount of drug included was not so much in the coprecipitated one. These results suggested that some interaction exists between the drug and β-CD in the freeze-dried product and the coprecipitated one.

Figure 22 shows the thermograms by the differential scanning calorimetry of mefenamic acid and β-CD, for example. The endothermic peak arround 505°K was observed in the intact drug as No. 1 and also the physical mixture of drug and β-CD as No. 2. However, the peak disappeared in the sample of freeze-dried mefenamic acid with β-CD, as No. 3. As a result, it was suggested that a new material

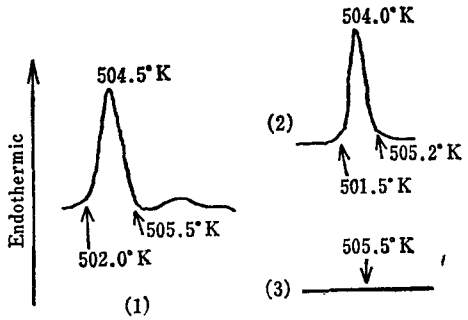


Fig. 22. Thermograms of Mefenamic Acid with β-CD.
(1) intact drug (2) physical mixture
(3) freeze-dried product

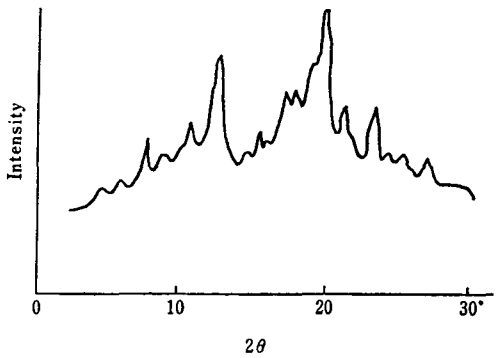


Fig. 24. X-ray Diffraction Pattern of Physical Mixture of Ibfenac and β-CD, both Separately Freeze-dried.

was formed by the freeze-drying of drug and β-CD together.

Figure 23 shows the X-ray diffraction patterns of ibfenac with β-CD, for example. The mixture was transformed to an amorphous one by freeze-drying. A similar result was observed in the case of that with α-CD. The coprecipitated one was obtained in crystalline state. Of course, the diffraction pattern in this case was different from that of the intact ibfenac.

Figure 24 shows the X-ray diffraction pattern of physical mixture of ibfenac and β-CD, both separately freeze-dried. So it is possible that the amorphous state shown in Fig. 23 is given when the drug and β-CD are freeze-dried together.

β-CD alone is also obtained in amorphous state by freeze-drying, while in crystalline state by recrystallization, as shown in Fig. 25. The two peaks of the broad diffraction pattern of freeze-dried β-CD are considered to be due to the sylindrical structure of the molecule, because similar peaks were observed at smaller interplanar distances in the case of α-CD. These two peaks in amorphous state might remain when CD was freeze-dried together with drug, as mentioned before. Exactly speaking, the cavity of CD seemed to be

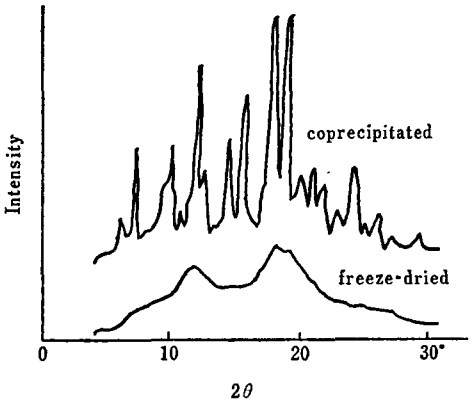


Fig. 23. X-ray Diffraction Patterns of Ibfenac with β-CD.

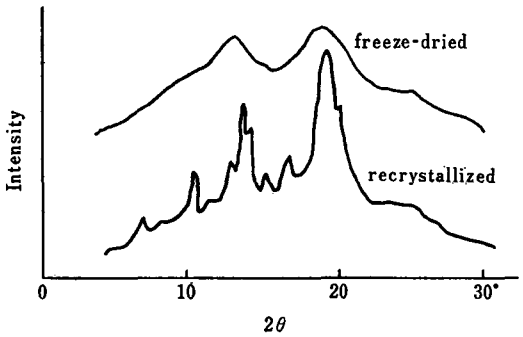


Fig. 25. X-ray Diffraction Patterns of β-CD.

made a little larger when the drug was included. Anyhow the cylindrical structure of CD might be kept in the freezedried inclusion compound as it was intact.

Figure 26 shows the dissolution curves of ketoprofen with β-CD for example. β-CD in the freeze-dried with drug was remarkably effective in increasing the dissolution rate.

Additionally, we prepared the mixtures, coprecipitates, freeze-dried samples of drugs with polyethylene glycol or polyvinyl pyrrolidone, and examined their dissolution rates. They all dissolved well. However, CD seemed preferable to the others because of the low hygroscopicity and the high fluidity of the product. Moreover, cyclodextrin may have an advantage over these kinds of synthetic polymers in the safety as the drug additive. In this point of view also, CD seems to afford a promising means for pharmaceutical preparations.

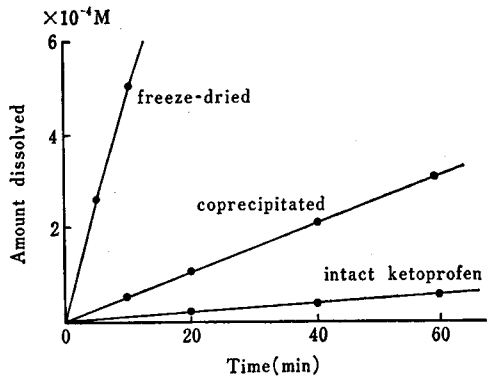


Fig. 26. Dissolution Curves of Ketoprofen with β-CD.

(Received in Nov. 10, 1976)

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